sensory information and to modify existing associations with appropriate deliberation.

Naturally, it is tempting to speculate about the mechanistic role of NCS-1 in plasticity. However, the NCS family of proteins is sizeable, diverse, and largely unexplored. *C. elegans* appears to have five NCS-related genes and humans have perhaps a dozen (Burgoyne and Weiss, 2001), with different members implicated in processes as diverse as guanylyl-cyclase regulation (Palczewski et al., 1994), K^+ channel modulation (An et al., 2000), and protein kinase inhibition (Chen et al., 1995). A role in control of synaptic strength (e.g., Pongs et al., 1993), though mechanistically not yet understood, is the most promising in explaining the current results. This NCS-1 function is likely to be in the interneuron AIY, but whether it functions pre- or postsynaptically, at what synapse, and by what biochemical mechanism are all unknown. The pump has been primed, but much remains to be investigated.

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Sleeper's Wake

Sleep has to be one of the Last Great Mysteries of animal physiology. For all we know about the phenomenon of sleep, we have, until recently, achieved little more than speculation as to what it does for the body. And yet sleep is as critical as any organ to health and well-being. Even short-term sleep deprivation has devastating effects throughout the body, on mental performance, immune function, endocrine function, and more. Long-term deprivation, whether induced experimentally in animals or induced by disease in humans, invariably leads to death. So our relative ignorance regarding the function of sleep, especially after years of studying its rhythms, its electrical signatures in the brain, its various stages, and its biochemistry, is all the more striking.

One of the proposed functions of sleep for which there is a considerable amount of evidence is memory consolidation. According to this view, sleep (and in particular REM sleep) is a period of little sensory input during which the brain rehearses or replays events or newly learned procedural tasks. The replay would then be required for these memories to be solidified in the brain. This idea is supported by a number of studies in both humans and animals showing that disrupting REM sleep reduces subsequent performance on simple memory tasks (Karni et al., 1994; Stickgold et al., 2000). Evidence of the replay itself comes from an elegant paper by Louie and Wilson (2001) recently published in Neuron and widely reported in the popular press. These authors recorded from several place neurons in the hippocampus as an animal ran a stereotyped path in a circular maze to receive a food reward. Given the repetitive path the animal took, the place neurons also fired in a stereotyped sequence as the animal repeatedly entered the place fields for each cell in turn. Following the maze running, the animals were allowed to sleep, and remarkably, the place neurons fired in sequences highly correlated to those recorded during the maze running. A similar effect has been observed in zebra finches in the period during which they learn their song. During sleep, the patterns of neuronal activity in a song-related nucleus (RA) are well correlated to the patterns present during song vocalization (Dave and Margoliash, 2000). While one must be cautious about interpreting these data as evidence for dreaming in animals or as evidence of memory consolidation, they are nevertheless suggestive in light of the consolidation hypothesis.

At the same time, however, the memory consolidation idea is not uncontroversial. In a recent review, Vertes and Eastman (2000) point out major difficulties with the supporting evidence. First, antidepressant drugs and some brainstem lesions suppress or even eliminate REM sleep, and yet cognitive performance in affected patients show little impairment. Second, only about half the animal studies looking for memory deficits after sleep deprivation have shown effects. Third, in many of these studies, sleep deprivation may have been confounded with stress. The sleep deprivation technique often used (placing the animal on a small platform above a pool of water) is itself stressful. The impairment of performance immediately following the deprivation period thus may be related to stress rather than sleep loss, and, indeed, some studies have shown that performance recovers some hours after the deprivation period. None of these findings are consistent with REM sleep being required for memory consolidation or retention.

Against the background of the controversy surrounding the role of sleep in memory, then, the paper by Frank et al. (2001) reported in this issue of *Neuron* is all the more interesting. These authors have not examined memory per se, but they examined a classical model of neuronal plasticity and found dramatic effects of short-

term sleep deprivation. The model used is the shift of ocular dominance induced in the kitten visual cortex by brief periods of monocular deprivation. In normal cats and kittens, the amount of inputs from the two eyes is roughly equal. Some neurons receive stronger input from one eye, some from the other. But overall, there are roughly equal numbers of neurons dominated by one eye or the other. Hubel and Wiesel (1970) showed in their now classical papers that closing one eye during the critical period early in a cat's life will dramatically shift the balance of ocular dominance so that only a few neurons with dominant input from the deprived eye remain. Once the critical period has passed, reversing the imbalance becomes extremely difficult. Whereas Hubel and Wiesel applied weeks of monocular deprivation to obtain the observed effects, more recently it has been shown that significant shifts in ocular dominance and in the underlying anatomical projections from the thalamus can be triggered by only a few hours of visual experience with one eye closed.

Frank et al. have taken advantage of this last property of the developing visual cortex to design a sensitive assay for the effects of sleep on plasticity. They closed one eye of 1-month-old kittens and kept them awake and alert for 6 hr of visual experience. In one group of these animals (the control group) measurements of ocular dominance were made immediately following this initial 6 hr period of monocular deprivation. Three experimental groups were given one of three different treatments for the 6 hr period following the initial deprivation: one group was allowed to sleep at will in total darkness for 6 hr; one group was kept awake in total darkness for 6 hr; and one was kept awake in the light for 6 hr, for a total of 12 hr of monocular deprivation in the light.

The control animals (6 hr of monocular deprivation) predictably showed a significant shift in ocular dominance toward the open eye. In the animals allowed to sleep for 6 hr in darkness following monocular deprivation, however, the shift was almost twice as large as the control and comparable to the group given 12 hr of monocular deprivation. Very few cells were left with dominant input from the deprived eye. The 6 hr delay between deprivation and recording was not in itself effective in enhancing the shift, however, since the animals that were kept alert in total darkness for 6 hr following the monocular deprivation period showed even less of a shift than control animals. Thus, in the absence of sleep, the changes that had occurred were partly lost. These effects were measured both in single-unit recording from multiple cells in the cortex and by optical imaging of the cortical surface.

The authors went on to explore whether it was the amount of REM or non-REM sleep that seemed to be determining how much plasticity was enhanced during the postdeprivation period. Surprisingly, the degree of ocular dominance shift correlates with a coefficient of 0.9 with the amount of non-REM sleep. The authors were not able to determine whether the shift correlated with REM sleep, however, since it is difficult to disrupt REM sleep in young cats without also affecting non-REM. Nevertheless, the message seems clear. During development, sleep allows the consolidation of changes in ocular dominance evoked by short-term experience; sleep deprivation prevents consolidation and even allows accumulated changes partly to reverse.

The mechanisms underlying these effects have yet to be discovered, but some suggestive results on this issue are already at hand. Non-REM sleep has been associated with increased release of neurotrophins (Krueger et al., 1999), growth factors (Cauter and Spiegel, 1999), and a generalized increase in protein synthesis in the brain (Ramm and Smith, 1990; Nakanishi et al., 1997).

The fundamental nature of sleep is underscored not only by the disastrous effects of long-term sleep deprivation, but by its presence in a large and disparate segment of the animal kingdom. Even flies sleep (Hendricks et al., 2000; Shaw et al., 2000) or at least exhibit a state of rest with many of the hallmarks of sleep, such as increased arousal thresholds, homeostasis of the state independent of the circadian clock, and modulation of molecular markers associated with sleep in mammals. This finding opens the possibility of exploring the mechanisms underlying sleep in one of the classical models of genetics and molecular biology. Findings such as those of Frank et al. suggest that a deeper understanding of the function of sleep may not be far off either.

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